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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,909	DIKSTEIN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *3-5,13(a-b),14,17,18(g-i)* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,6,12,13(c-d),15-16,18(e-f),19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1-2, 6, 12-13, 15-16, 18-19, species inflammation in Paper No. 13 is acknowledged. The traversal is on the ground(s) that 1) Group I and XVI should be examined together because the search of group XVI would encompass a search for antisense molecules of SEQ ID NO:1 and methods of promoting apoptosis, and it would not be undue search burden for the Examiner, and 2) the polynucleotides encoding $TAF_{II}105$ are not taught or suggested by the cited references of Dikstein et al, 1996 and US 5,710025. This is not found persuasive because of the following reasons: 1) It is noted that due to the language "comprises", the claimed DNA molecule of claim 1 encompasses a nucleic acid sequence of any length, provided it comprises a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said polypeptide. Further, since claim 1 is not drawn to a specific nucleotide sequence with a specific sequence identification number, i.e. SEQ ID NO:1, claim 1 encompasses any nucleotide sequence, which is deduced from a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, using degenerate codon, wherein said fragment has a dominant negative effect on the normal biological activity of said polypeptide. The specification discloses that the N-terminal fragment of SEQ ID NO:2, amino acids 1 to 552, has dominant negative effect on the normal biological activity of the full length $TAF_{II}105$ polypeptide of SEQ ID NO:2 (p.4, lines 4-21). From MPSRCH sequence similarity search, Dikstein et al, 1996, and US 5,710, 025 teach a human TAFII 105 sequence, which is 99.9% similar to the

claimed polypeptide of SEQ ID NO:2, from amino acids 1 to 801, with a single mismatch at amino acid 730 (MPSRCH sequence similarity search report, 2003, us-09-763-909-2.rsp, pages 1-2, and us-09-763-909-2.rai, pages 1-2). Moreover, Dikstein et al, 1996, teach amino acids 1-552 fragment for use in antibody production (p.145, paragraph under Antibodies and immunoprecipitations). Thus an inherent nucleic acid sequence encoding amino acids 1-552 fragment, deduced from any combination of nucleotides due to degeneracy of the codon, would encompass the claimed polynucleotide fragment encoding amino acids 1-552 of the $TAF_{II}105$ polypeptide of SEQ ID NO:2. Moreover, US 5,710, 025 teach a nucleic acid encoding a human TAFII 105 sequence, which is 99.9% similar to the claimed polypeptide of SEQ ID NO:2, from amino acids 1 to 801, with a single mismatch at amino acid 730 , and thus would encompass the claimed polynucleotide fragment. Thus as clearly stated in previous Office action, the technical feature of group I does not make a contribution over the prior art, and thus the groups I and XVI do not related to a single general inventive concept, and are different inventions.

The requirement is still deemed proper and is therefore made FINAL.

After review and reconsideration, groups II-V are rejoined with group I, as species, and groups VII-X are rejoined with group VI as species.

Accordingly, claims 1-2, 6, 12, 13(c-d), 15-16, 18((e-f) and 19 are examined in the instant application, wherein claims 1-2, 6, 12, 13(c-d), 15, 18(e-f) and 19 are examined only to the extent of the DNA sequence of SEQ ID NO:1, a DNA sequence encoding the TAFII 105 polypeptide of SEQ ID NO:2, and a fragment thereof, wherein

said fragment has a dominant negative effect on the normal biological activity of said TAFII 105 polypeptide, an expression vector comprising said polynucleotide fragment, and an antisense of SEQ ID NO:1. It is noted that the species cancer treatment is rejoined with the species treatment of inflammation, and are thus examined in the instant application. Claims 3-5, part of claim 13 (c), drawn to a DNA sequence encoding a modified fragment of the TAFII 105 polypeptide of SEQ ID NO:2, and claim18(g) are withdrawn from consideration as being drawn to non-elected species. Claims 13(a-b) and 18(h-i) are withdrawn from consideration as being drawn to non-elected inventions.

OBJECTION

1. Claims 1, 13, 15, 18 are objected to because part of claims 1, 13, 15, 18 are drawn to non-elected inventions.

2. Claim 2 is objected to for the use of the language "derived", because it is not clear how the fragment is "derived".

3. Claim 18 is objected to because there is no items (a-d) preceding items (e-i) of claim 18.

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

Claims 1-2, 6, 13(c), 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 6, 13(c) and 15-16, are indefinite for the use of the language "dominant negative effect" in claims 1, 13, 15, which does not set forth the metes and bound of the patient protection desired. This rejection could be obviated by amending claim 1 for example to replace "has dominant negative effect on" with "inhibits".

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, SCOPE

1. Claims 1-2, 6, 13(c), 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment decreases the basal activity of NF-κB, does not reasonably provide enablement for a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the "normal biological activity" of said $TAF_{II}105$ polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-2, 6, 13(c), 15-16 are drawn to a DNA molecule comprising a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the "normal biological activity" of said $TAF_{II}105$ polypeptide, a pharmaceutical composition comprising said DNA molecule, and an expression vector comprising said DNA molecule. Said fragment is derived from the N-terminal domain of SEQ ID NO:2

The specification discloses that "normal biological activity" of the $TAF_{II}105$ polypeptide is mediation by $TAF_{II}105$ polypeptide of the activation of anti-apoptosis genes by NF-κB (p.4, lines 4-6). The specification discloses that in co-transfected cells, full length $TAF_{II}105$ polypeptide increases the basal activity of NF-κB and p65 (p.16, last paragraph), whereas a sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide strongly inhibits the constitutive basal activity of NF-κB (p.18, second paragraph). The specification discloses that after transfection with full length $TAF_{II}105$ or p65 alone, or a combination of full length $TAF_{II}105$ and p65, no effect on cell apoptosis is observed, whereas co-transfection of DNA sequence encoding a sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide and p65 results in apoptosis of the host cell (p.20, first paragraph, especially lines 10-16). The specification further discloses that NF-κB can activate either anti-apoptotic or apoptotic genes, and p65 can produce both anti-apoptotic or apoptotic signals (p.20, first paragraph).

One cannot extrapolate the teaching of the specification to the scope of the claims. It is unpredictable that full length$TAF_{II}105$ polypeptide mediates the activation of anti-apoptosis genes by NF-κB, because of the following reasons: Although after transfection with full length $TAF_{II}105$ or p65 alone, or a combination of full length $TAF_{II}105$ and p65, no effect on cell apoptosis is observed, and although full length $TAF_{II}105$ polypeptide increases the basal activity of NF-κB, one cannot extrapolate that full length$TAF_{II}105$ polypeptide mediates the activation of anti-apoptosis genes by NF-κB, because the absence of cell apoptosis does not mean that anti-apoptosis genes are

activated, and because it is well known in the art that NF-κB has multiple activities, and not just activation of pro- or anti-apoptosis genes. Moreover, even if the anti-apoptosis event occurs, full length lengthTAF$_{II}$105 polypeptide activates both NF-κB and p65, wherein both NF-κB and p65 can have an effect on anti-apoptotic signals, and thus one cannot predict that the anti-apoptosis would be derived from activation of which of the polypeptide NF-κB or p65 or both.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

2. Claims 13, 15-16, 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cDNA sequence encoding the TAF$_{II}$105 polypeptide of SEQ ID NO:2, or SEQ ID NO:1 or a fragment thereof, wherein said fragment comprises a nucleotide sequence encoding a fragment of the TAF$_{II}$105 polypeptide of SEQ ID NO:2, and wherein said fragment decreases the basal actitivity of NF-κB, does not reasonably provide enablement for a "pharmaceutical composition for inducing an apoptotic process in pathological cells, or for treating inflammation", comprising a DNA sequence encoding the TAF$_{II}$105 polypeptide of SEQ ID NO:2, or SEQ ID NO:1 or a fragment thereof, wherein said fragment comprises a nucleotide sequence encoding a fragment of the TAF$_{II}$105 polypeptide of SEQ ID NO:2, and wherein said fragment has a dominant negative effect on the normal biological activity of said TAF$_{II}$105 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 13(c), 15, 16 are drawn to a pharmaceutical composition for inducing an apoptosis process in pathological cells, which is cancer treatment, comprising a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the "normal biological activity" of said $TAF_{II}105$ polypeptide. Claims 18-19 are drawn to a pharmaceutical composition for treating inflammation, comprising a DNA sequence encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2 , or SEQ ID NO:1.

It is noted that inherent in a pharmaceutical composition is the *in vivo* use thereof. Thus the claims encompass 1) a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, and wherein said DNA sequences are used in gene therapy for treating cancer and 2) a DNA sequence encoding the full length $TAF_{II}105$ polypeptide of SEQ ID NO:2, or SEQ ID NO:1, wherein said DNA sequences are used in gene therapy for treating inflammation.

The specification discloses that co-transfection of a DNA sequence encoding a sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide of SEQ ID NO:2 and p65 results in apoptosis of the host cell (p.20, first paragraph, especially lines 10-16). The specification further discloses that in certain experiments, the amount of the expressed sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide ($TAF_{II}105\ \Delta\ C$) is insufficient to affect cell viability when cotransfected with p65 (p.18, lines 19-24). In other words, depending on the amount of expressed $TAF_{II}105\ \Delta\ C$, cell apoptosis might not occur. The specification discloses contemplation of using the

claimed polynucleotide fragments for apoptosis promoting, for example for treating cancer (p.4, last paragraph, bridging p.5).

The specification discloses contemplation of using the claimed full length polynucleotides as "apoptosis prevention", for situation such as undesirable induction of apoptosis in autoimmune diseases, inflammatory processes and viral or bacterial infections (p.5 last paragraph, bridging p.6).

Concerning treating cancer by a sequence encoding a sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide ($TAF_{II}105$ Δ C), one cannot extrapolate the teaching of the specification to the scope of the claims, because there is no correlation between *in vitro* induction of apoptosis by $TAF_{II}105$ Δ C in transfected cells and *in vivo* treatment of cancer, for the following reasons: a) In transfected cells, both $TAF_{II}105$ Δ C and p65 artificially overexpressed, and could be responsible for artificial conditions in interaction between $TAF_{II}105$ Δ C and p65. It is well known in the art the outcome of apoptosis could depend on the intracellular concentrations of polypeptides effecting cell death or survival. For example, it is well known in the art that the cellular concentration of members of Bcl-2 family is directly related to whether a cell will respond to an apoptotic signal, and that, for example, resistance of mature thymocytes to apoptotic signals correlates with high expression level of Bcl-2 protein, and overexpression of a cell death promoter BAD would counter the death inhibitory activity of Bcl-XL (Oltvai et al, 1994, Cell, 79: 189-192). Further, as disclosed by the specification, in certain experiments, the amount of the expressed sequence consisting of amino acids 1-552 of the $TAF_{II}105$ polypeptide ($TAF_{II}105$ Δ C) is insufficient to affect

cell viability when cotransfected with p65 (p.18, lines 19-24), and one cannot predict whether the amount of expressed $TAF_{II}105$ Δ C and p65 would be adequate *in vivo* for inducing apoptosis (see gene therapy issue below), b) *in vitro* conditions are not the same as *in vivo* conditions with feed back mechanisms of the host and cell-cell interaction, and c) cells *in vitro* do not have the same characteristics and responses as cells in *in vivo* conditions.

The enablement of the claimed invention appears to be based solely on *in vitro* data. There is however no correlation between *in vitro* induction of apoptosis by $TAF_{II}105$ Δ C in transfected cells and *in vivo* treatment of cancer. Kimmel et al.(J. Neurosurg, 66:161-171, 1987) teach that *in vitro* assays cannot easily assess host and cell-cell interactions that may be important, and cannot duplicate the complex conditions of *in vivo* therapy. Further, characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and

specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a

normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, inhibition of apoptosis by a DNA sequence consisting of a sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, $TAF_{II}105$ Δ C, and p65 *in vitro* would be in any way correlated with treating inflammation.

Thus the claims as drawn to a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, $TAF_{II}105$ Δ C, and wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, as a therapeutic agent for treating cancer do not read on induction of apoptosis in cells co-transfected with a DNA sequence consisting of a sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2 and p65 *in vitro*.

Moreover, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that

researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed polynucleotide fragments would be effective in treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the

claimed polynucleotide fragments would be effective in treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Further, the efficacy of gene therapy for treating of cancer or inflammation using the claimed polynucleotide sequences or fragments thereof, is unpredictable. The state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells

and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

3. Claims 12, 13(d) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antisense of SEQ ID NO:1, which is capable of inhibiting its expression *in vitro* does not reasonably provide enablement for an antisense of SEQ ID NO:1, which is capable of inhibiting its expression *in vivo*, or a pharmaceutical composition for inducing an apoptotic process in pathological cells which is treatment of cancer. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims.

Claims 12, 13(d) are drawn to a DNA molecule directing expression of an antisense RNA sequence of SEQ ID NO:1, or a part thereof, and which is capable of inhibiting its expression *in vivo*, and a pharmaceutical composition for inducing an apoptotic process in pathological cells, which is treatment of cancer, comprising said DNA sequence.

The claims encompass an antisense of SEQ ID NO:1, which can be used *in vivo* for inhibiting the expression of SEQ ID NO:1 and treating cancer.

The specification discloses that transient expression of antisense $TAF_{II}105$ reduces the endogenous level of the $TAF_{II}105$ protein (p.19,last paragraph).

One cannot extrapolate the teaching of the specification to the scope of the claims because it was well known in the art at the time the invention was made that the status of the field of gene therapy in humans was unpredictable, *supra*. Further, Wang et al (PNAS, 1995, 92:3318-3322) specifically teach that therapeutic applications of antisense oligonucleotides are currently limited by their low physiological stability, slow cellular uptake and lack of tissue specificity (p. 3318, para 1). Problems with cellular uptake of antisense oligonucleotides are difficult to solve because endogenous uptake pathways generally have insufficient capacity to deliver the quantities of antisense oligonucleotides required to suppress gene expression and intracellular delivery and tissue specificity remain major obstacles to the implementation of antisense drugs in the treatment of human disorders (p. 3318, para bridging cols 1 and 2). Moreover, in the

field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many concerns. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

4. Claims 1-2, 6, 13(c) , 15-16, 18 (e-f) and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cDNA molecule encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2, or SEQ ID NO:1 and a fragment thereof, does not reasonably provide enablement for a "DNA molecule" encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2, or a "DNA molecule" comprising SEQ ID NO:1 and a fragment thereof. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-2, 6, 13(c), 15, 16 are drawn to a DNA molecule comprising a nucleotidesequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, a vector comprising said DNA molecule, and a pharmaceutical composition comprising said DNA sequence, for inducing an apoptosis process in pathological cells, which is cancer treatment. Claims 18(e-f)-19 are drawn to a pharmaceutical composition for treating inflammation, comprising a DNA sequence encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2 , or a DNA molecule comprising the DNA sequence of SEQ ID NO:1.

Claims 1-2, 6, 13(c) , 15-16, 18 (e-f) and 19 encompass genomic DNA molecule comprising a DNA sequence encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2 , or a genomic DNA molecule comprising the DNA sequence of SEQ ID NO:1.

The specification discloses $TAF_{II}105$ prepared as described previously by Dikstein et al , 1996 (p. 12, lines 16-18), and a $TAF_{II}105$ polynucleotide of SEQ ID NO:1, which is 99.9% similar to the $TAF_{II}105$ cDNA sequence described by Dikstein et al, Cell, 1996, 87: 137-146, IDS # AF of paper No:9, on 01/31/02, as shown from MPSRCH sequence similarity search, (MPSRCH sequence similarity search report, 2003, us-09-763-909-1.rge, pages 1-2). There is no description of a genomic DNA sequence encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2 in the specification.

The specification fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: 1 or fragments thereof.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant

for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2, 13(c), 15-16 are rejected under 35 U.S.C. 102(b or e) as being anticipated by Dikstein, R et al, Cell, 1996, 87: 137-146, IDS # AF of paper No:9, on 01/31/02, and US 5,710,025, IDS # AA of paper No:9, on 01/31/02.

Claims 1-2 are drawn to a DNA molecule "comprising" a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, and wherein said fragment is derived from the N-terminal domain of SEQ ID NO:2. Claims 13(c), 15, 16 are drawn to a pharmaceutical composition for inducing an apoptosis process in pathological cells, which is cancer treatment, "comprising" a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide.

Due to the indefinite language of claim 1, 13(c), 15, it is assumed for the purpose of compact prosecution that the claimed DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment inhibits the normal biological activity of said $TAF_{II}105$ polypeptide.

Further, claims13(c), 15, 16 recite the claimed DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, formulated as a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims read on the ingredient *per se*, which is a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide.

It is noted that due to the language "comprises", the claimed DNA molecule of claim 1 encompasses a nucleic acid sequence of any length, provided it comprises a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said polypeptide. Further, since claim 1 is not drawn to a specific nucleotide sequence with a specific sequence identification number, i.e. SEQ ID NO:1, claim 1 encompasses any nucleotide sequence, which is deduced from a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, using degenerate codon, wherein said fragment has a dominant negative effect on the normal biological activity of said polypeptide.

The specification discloses that the N-terminal fragment of SEQ ID NO:2, amino acids 1 to 552, has dominant negative effect on the normal biological activity of the full length $TAF_{II}105$ polypeptide of SEQ ID NO:2 (p.4, lines 4-21).

Dikstein et al, 1996, and US 5,710, 025 teach a human TAFII 105 sequence, which is 99.9% similar to the claimed polypeptide of SEQ ID NO:2, from amino acids 1 to 801, with a single mismatch at amino acid 730, as shown from MPSRCH sequence similarity search, (MPSRCH sequence similarity search report, 2003, us-09-763-909-2.rsp, pages 1-2, and us-09-763-909-2.rai, pages 1-2). Moreover, Dikstein et al, 1996, teach amino acids 1-552 fragment for use in antibody production (p.145, paragraph under Antibodies and immunoprecipitations). Thus an inherent nucleic acid sequence encoding amino acids 1-552 fragment, deduced from any combination of nucleotides due to degeneracy of the codon, would encompass the claimed polynucleotide fragment encoding amino acids 1-552 of the $TAF_{II}105$ polypeptide of SEQ ID NO:2. Moreover, US 5,710, 025 teach a nucleic acid encoding a human TAFII 105 sequence, which is 99.9% similar to the claimed polypeptide of SEQ ID NO:2, from amino acids 1 to 801, with a single mismatch at amino acid 730 , and thus would encompass the claimed polynucleotide fragment.

The references do not specifically teach that the encompassed, encoded fragment has a dominant negative effect on the normal biological activity of the $TAF_{II}105$ polypeptide. However, the claimed DNA molecule appears to be the same as the prior art polynucleotide sequences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product

of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dikstein, R et al, *supra*, and US 5,710,025, *supra,* in view of US Patent No. 4,889,806.

The claim is drawn to an expression vector containing a DNA molecule "comprising" a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, and wherein said fragment is derived from the N-terminal domain of SEQ ID NO:2, and DNA sequences required for its expression.

Dikstein, R et al, and US 5,710,025 disclose as set forth above but differ from the instant invention in that they do not disclose an expression vector containing a DNA molecule "comprising" a nucleotide sequence encoding a fragment of the $TAF_{II}105$

polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of said $TAF_{II}105$ polypeptide, and wherein said fragment is derived from the N-terminal domain of SEQ ID NO:2, and DNA sequences required for its expression.

US Patent No. 4,889,806 teach that with the advent of recombinant DNA and molecular cloning technology it is now conventional to transfer genetic information into plasmids or vectors constructed *in vitro* and then transferred into host cells and clonally propagated (col 1, lines 18-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the polynucleotide of Dikstein, R et al, or US 5,710,025 with the methods of US Patent No. 4,889,806 because US Patent No. 4,889,806 specifically teaches that it is conventional to transfer genetic materials into plasmids or vectors and then transfer the plasmids or vectors into host cells and clonally propagate the genetic material.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

March 20, 2003